REMARKS/ARGUMENTS

The foregoing amendments in the specification and claims are of a formal nature, and do not add new matter.

Prior to the present amendment, Claims 28-47 were pending in this application and were rejected on various grounds. With this amendment, Claims 28-32, 34-37 and 41-43 have been canceled without prejudice, Claims 33, 38-39 and 44 have been amended to clarify what Applicants have always regarded as their invention., and new Claims 48-53 have been added.

Claims 33, 38-40 and 44-53 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

The amendments to the specification and claims are fully supported by the specification and claims as originally filed and do not constitute new matter. In addition, new Claims 48-53 are fully supported by the specification as originally filed. Support for new Claims 48-53 can be found at least on page 192, line 35 to 193, line 2, on page 193, lines 14-17, on page 282, lines 12-19 and on page 308, line 38 to page 309, line 7 of the specification.

Applicants thank the Examiner for entering the amendments filed on December 12, 2001 and August 29, 2002.

Specification

In response to the Examiner's request, the specification has been amended to remove embedded hyperlink and/or other form of browser-executable code.

Oath/Declaration

The Examiner alleges that the oath or declaration of the present application is defective because non-initialed and/or non-dated alteration have been made to the oath or declaration (for inventor Dan Eaton) and requires Applicants to submit a new oath or declaration in compliance with 37 C.F.R. §1.67(a). Applicants respectfully disagree.

Applicants respectfully submit that 37 C.F.R. §1.52(c)(1) states:

> (c)(1) Any interlineations, erasure, cancellation or other alteration of the application papers filed must be made before the signing of any accompanying

oath or declaration pursuant to §1.63 referring to those application papers and should be dated and initialed or signed by the applicant on the same sheet of paper. (Emphasis added).

Further, M.P.E.P. §605.04(a) states, "Any changes made in ink in the application or oath prior to signing should be initialed and dated by the applicants prior to execution of the oath or declaration." The previously submitted declaration included the change of address in ink by Dr. Dan Eaton. Dr. Eaton properly initialed below the change made to his address and dated the declaration. Therefore, Applicants respectfully submit that a new oath or declaration in compliance with 37 C.F.R. §1.67(a) is not required and request the Examiner to reconsider and withdraw the objection.

Priority Determination

Applicants rely on the gene amplification assay (Example 143) for patentable utility which was first disclosed in U.S. Provisional Application No. 60/162,506, filed October 29, 1999, priority to which has been claimed in this application.

Accordingly, the present application is entitled to at least the October 29, 1999 priority for subject matter defined in Claims 33, 38-40 and 44-53.

Claim Rejections – 35 U.S.C. §101

Claims 28-47 are rejected under 35 U.S.C. §101, allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." The Examiner asserts that "the instant specification does not disclose any data for the any activity of the protein of the SEQ ID NO:282 amino acid sequence. There are no well-established utilities for newly discovered biological molecules." Examiner further alleges that the specification asserts numerous utilities for the claimed polynucleotides which are not specific or substantial. (See pages 4-17 of the instant Office Action). In particular, the Examiner notes that "the instant specification does not disclose any specific disease state wherein there is a change in the SEQ ID NO:281 polynucleotide sequence expression levels or forms."

Applicants respectfully disagree with and traverse the rejection.

Applicants submit that the cancellation of Claims 28-32, 34-37 and 41-43 renders the rejection of these claims moot. Claims 33, 38-40 and 44-53 have patentable utility for the reasons discussed below.

Legal Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re* Langer, 503 F.2d 1380,1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re* Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re* Irons, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. §101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is *a preponderance of the totality of the evidence* under consideration. *In re* Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, shifts the burden of rebuttal to the applicant. The issue will then be decided on the totality of evidence.

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly

is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient*, at least with regard to defining a "substantial" utility." M.P.E.P. §2107.01, emphasis added. Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P, §2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the applicant's assertions." M.P.E.P. §2107 II(B)(1)(ii). Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Revised Interim Utility Guidelines Training Materials, 1999.

Proper Application of the Legal Standard

Applicants submit that the invention defined by the presently amended claims has specific, substantial and credible utility for the nucleic acids encoding the PRO1780 polypeptide.

As mentioned above, Applicants rely on the gene amplification data for priority and to establish patentable utility for the PRO1780 polypeptide. This data was first disclosed in U.S. Provisional Application Serial No. 60/162,506, filed October 29, 1999, the priority of which is claimed in the present application. Hence, the effective filing date of the present application is October 29, 1999. Further, the Examiner has admitted that out on page 12 of the instant

application that the nucleic acid encoding the PRO1780 polypeptide is amplified in three primary lung tumors (LT4, LT7 and LT22).

It is well known in the art at the time the invention was made that gene amplification is an essential mechanism for oncogene activation. The gene amplification assay is well-described in Example 143 of the present application, the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 8, including primary lung and colon tumors of the type and stage indicated in Table 7. As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control. Gene amplification was monitored using real-time quantitative TaqMan PCR. Table 8 shows the resulting gene amplification data. Further, Example 143 explains that the results of TaqMan™ PCR are reported in ΔCt units, wherein one unit corresponds to one PCR cycle or approximately a 2-fold amplification relative to control, two units correspond to 4-fold amplification, 3 units to 8-fold amplification etc. The specification discloses that the nucleic acids encoding PRO1780 had ΔCt value of > 1.0, which is **more than 2-fold increase**, for primary lung tumors LT4, LT7 and LT22.

Because amplification of the nucleic acid encoding PRO1780 occurs in various lung tumors, it is likely associated with tumor formation and/or growth. As a result, antagonists (*e.g.*, antibodies) directed against PRO1780 would be expected to be useful in cancer therapy.

It is well known that gene amplification occurs in most solid tumors, and generally is associated with poor prognosis.

In support, Applicants submit a Declaration by Dr. Audrey Goddard with this response and particularly draw the Examiner's attention to page 3 of the declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a

> normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

The attached Declaration by Audrey Goddard clearly establishes that the TaqMan real-time PCR method described in Example 143 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The facts disclosed in the Declaration also confirm that based upon the gene amplification results, one of ordinary skill would find it credible that PRO1780 is ***a diagnostic marker of human lung cancer***.

The Examiner also asserts that "chromosome aberrations known as aneuploidy are commonly observed in tumors", thus "[w]hether aneuploidy is a cause or consequence of the tumor is unclear."

In response, Applicants submit a Declaration by Dr. Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the present application, to demonstrate the credibility of the gene amplification assay. In particular, Dr. Ashkenazi is in opinion that gene amplification of a gene, whether by aneuploidy or any other mechanism, is still useful as a diagnostic marker. As a result, the present gene amplification assay is a well-controlled experiment and give rise to data of biological significance. As Dr. Ashkenazi explains,

> An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

Applicants note that The Examiner further alleges that "gene copy number does not predictably influence protein levels." (See page 12 of the instant Office Action). Applicants respectfully submit that present application is only directed to nucleic acids. Therefore, Applicants further submit that since the claims in the present application s are only directed to polynucleotides and not polypeptides, this rejection is moot.

Nevertheless, Applicants maintain that the utility is provided for the polypeptides and antibodies in the present application.

In view of the above, Applicants have demonstrated a credible, specific and substantial asserted utility for the polynucleotide encoding the PRO1780 polypeptide. The data shown in the present application clearly demonstrates that the nucleic acid of SEQ ID NO:281 that encodes PRO1780 is amplified in lung cancer. Based on this information one skilled in the art at the effective priority date of this application would have accepted that the nucleic acids encoding PRO1780 meet the utility requirement of the 35 U.S.C. §101 as a diagnostic marker for lung cancer. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of under 35 U.S.C. §101.

Claim Rejections Under 35 U.S.C. §112, First Paragraph (Enablement)

Claims 28-47 are also rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility ..., one skilled in the art would not know how to use the claimed invention".

Applicants respectfully disagree and traverse the rejection.

Applicants submit that the cancellation of Claims 28-32, 34-37 and 41-43 renders the rejection of these claims moot.

In response to the previous "lack of utility" rejection, Applicants have shown that the claimed polynucleotides do have at least one patentable utility, namely utility in the diagnosis of lung tumor. Further, based on the instant disclosure, which details how to make and use the claimed nucleic acids and the advanced knowledge in the art at the time of filing, one skilled in the art would know exactly how to make and use the claimed nucleic acids for the diagnosis of lung cancer; for example, by using diagnostic methods based on hybridization to such amplified sequences.

Accordingly, Applicants submit that Claims 33, 38-40 and 44-53 satisfy the enablement requirement and Applicants respectfully request the Examiner to reconsider and withdraw the rejection of under 35 U.S.C. §112, first paragraph.

Claim Rejection Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 28-47 are rejected under 35 U.S.C. §112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention."

Applicants respectfully disagree and traverse the rejection.

Applicants submit that the cancellation of Claims 28-32, 34-37 and 41-43 renders the rejection of these claims moot. Furthermore, the Examiner has admitted that the polynucleotide sequence set forth in SEQ ID NO:281 meets the written description provision of 35 U.S.C. §112, first paragraph. (See page 25 of the instant Office Action).

Therefore, Applicants respectfully submit that Claims 33, 38-40 and 44-53 satisfy the written description requirement, such that one skilled in the art would readily recognize that the Applicants were in the possession of the invention claimed at the effective filing date of this application. Hence, the present rejection should be withdrawn.

Claim Rejections Under 35 U.S.C. §112, First Paragraph (Enablement)

Claims 28-47 are also rejected under 35 U.S.C. §112, first paragraph, allegedly for "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." The Examiner specifically notes that "Applicants has deposited the polypeptide encoded by cDNA deposited under ATCC accession number 203467 (pp. 517-519 of the specification), but there is no indication in the specification as to public availability."

Applicants respectfully disagree and traverse the rejection.

Applicants submit that the cancellation of Claims 28-32, 34-37 and 41-43 renders the rejection of these claims moot.

In response, Applicants respectfully submit that the specification clearly discloses that the deposit was made under the Budapest Treaty and clearly provides the accession number for the deposit, the date of the deposit, the description of the deposited material, and the name and address of the depository starting on page 517, line 1 of the specification.

In addition, the specification has been amended to recite that the deposit will be maintained "for 30 years from the date of deposit and for at least five (5) years after the most recent request for the furnishing of a sample of the deposit received by the depository" and to recite that "all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the pertinent U.S. patent."

Accordingly, Applicants believe that the present rejection should be withdrawn.

Claim Rejections – 35 U.S.C. §112, Second Paragraph

Claims 28-33, 35-37 and 41 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleges that the specification does not clearly indicate where the extracellular domain is.

Claims 41-43 are further rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleges that the term "stringency" in Claim 42 is relative term which renders the claim indefinite.

Applicants respectfully disagree and traverse the rejection.

Without acquiescing to the Examiner's position in the current rejections, and without prejudice to further prosecution of the subject-matter in one or more continuation or divisional applications, Applicants submit that the cancellation of Claims 28-32, 34-37 and 41-43 renders the rejection of these claims moot.

Further, since the terms "extracellular domain" and "extracellular domain lacking its associated signal peptide" is no longer present in Claim 33 (and, as a consequence, those claims dependent from the same), the rejection is believed to be moot, and should be withdrawn.

Claim Rejections – 35 U.S.C. §102

Claims 28-39 and 41-47 are rejected under 35 U.S.C. §102(a) as being anticipated by McCarthy *et al.* (WO 00/77239), with a publication date of December 21, 2000. The Examiner alleges that McCarthy *et al.* disclose a polypeptide that is 100% identical to the polypeptide of

SEQ ID NO:282 and antibodies thereof.

Applicants respectfully disagree and traverse the rejection.

Applicants submit that the cancellation of Claims 28-32, 34-37 and 41-43 renders the rejection of these claims moot.

As discussed above, the pending claims of the instant application are entitled to the effective filing date of October 29, 1999, and hence, the publication by McCarthy *et al.* is not a prior art under 102(a) since its publication date is after the effective priority date of this application. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection under 35 U.S.C. §102(a).

CONCLUSION

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2830 P1C60**)

Respectfully submitted,

Date: January 14, 2005

By: _____
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